

Beating the superbugs

We may have a breakthrough in fighting “one of the greatest threats to human health”

PHILIP BALL

If there is some small comfort to be found amid the rise of antibiotic-resistant bacteria, it's that the severity of the problem is now common knowledge. The public vote that decided the target of the Longitude Prize 2014—a UK competition that channelled £10m towards a “grand challenge”—selected “preventing antibiotic resistance” from a shortlist of six worthy candidates.

No one imagines that this prize will solve the problem, but its specific objective—a point-of-care diagnostic test that would determine whether a patient's condition warrants antibiotics, and if so, which ones—would be extremely valuable. Indiscriminate use of general-purpose antibacterial drugs is at the root of the rapid spread of pathogenic bacteria resistant to them, such as the notorious MRSA (methicillin-resistant *Staphylococcus aureus*).

But as well as better procedures for identifying infections and prescribing antibiotics, we desperately need new ones if we are to avoid calamitous consequences. In recent years, the supply of new antibiotics that work on resistant strains has almost dried up. Now, however, scientists are finding new ways of prospecting for them in nature, as well as reshuffling the ones we have already in the hope of finding better drugs.

Before antibiotics were discovered in the 1930s, a simple infection could be fatal and any surgical procedure was perilous. Antibiotics have added an estimated 20 years to average life expectancy. As resistance spreads, scientists and clinicians are not exaggerating when they talk about the “potentially catastrophic consequences of inaction,” as the Centres for Disease Control and Prevention in the United States has put it. Biochemist Gerry Wright of McMaster University in Hamilton, Canada, warns that we risk “drifting back to a pre-antibiotic era where infectious diseases predominate as the cause of death”: he points out that in 1925, 56 per cent of all deaths in Canada were caused by infection, while in 2009 that figure was 3 per cent. The World Economic Forum has identified antibiotic resistance as one of the greatest threats to human health; it is a much scarier crisis than Ebola. Unlike any single disease, says Kim Lewis of the Antimicrobial Discovery Centre of Northeastern University in Boston, resistant bacterial pathogens “potentially threaten our society.”

But this is a complex problem. The challenges aren't purely scientific, but are connected to medical practice, livestock rearing (blanket use of antibiotics in intensive animal husbandry), the economics of the pharmaceutical industry and

socioeconomic differences between nations—poorer countries will suffer the most. The rate at which new antibiotics are discovered has slowed, but there are several reasons for this and a tranche of new drugs wouldn't solve the problem by itself. How bleak is the outlook?

Penicillin was famously discovered by accident, and many of the subsequent families of antibiotics found during the “golden age” of the 1940s to the 1960s were also the product of blind searches. Nature is a treasure trove of resources because other organisms have to deal with bacterial pathogens too. Plants and animals have evolved anti-microbial compounds that ward off infection and even bacteria themselves synthesise chemicals deadly to competing species, killing off rivals for limited supplies of nutrients. This makes soils and natural waters good hunting grounds for new antibiotics, which chemists might then tinker with to improve their performance. But the search has been hampered because many bacteria in the wild don't thrive in laboratory culture dishes: there's a mass of microbial “dark



Philip Ball is a science writer and Associate Editor of *Prospect*. He blogs about science at www.prospectmagazine.co.uk



matter” out there that we can’t easily investigate. “Researchers have seen this [dark matter] as a potential if not unlimited source of antimicrobials,” says Lewis.

Antibiotics use several tricks to stop pathogenic bacteria from multiplying. Some actually kill the bugs, others just stop or slow down reproduction. Some are molecules that insert themselves into bacterial cell walls and make them leaky, so that the bacteria can’t maintain the delicate balance of chemical ingredients that they need to function. Some disable enzymes that are crucial for the health of the bacterium. Some are “broad spectrum” agents, attacking bacteria indiscriminately; others are “narrow spectrum,” aimed at specific types. The first natural antibiotic, penicillin, discovered in 1928 by Alexander Fleming and developed into a useful drug a decade later by Howard Florey and Ernst Chain, is a broad-spectrum antibiotic that disrupts a bacterium’s ability to maintain its protective cell wall. (It’s often overlooked that completely synthetic antibiotics—so-called sulfa drugs—were being used in the 1930s before penicillin came into its own.)

Penicillin is little used today because many bacteria are resistant to it. This is a straightforward consequence of evolution—indeed it is one of the best demonstrations of Darwinian natural selection. When individual cells in a bacterial population acquire, by chance, a gene mutation that encodes a molecular strategy for evading the damage that an antibiotic wreaks, it has a reproductive advantage; the gene then spreads through the population. This process is dismayingly fast, both because bacteria reproduce rapidly and because they share useful genes in a process called horizontal gene transfer, which can pass a function like antibiotic resistance between species.

The more exposure bacterial populations get to antibiotics, the stronger is the selective pressure that promotes the rise of resistance. It’s a little like shouting at a classroom of unruly children: if you do it too often, rather than making it a strategy of last resort, it loses its shock value and has no effect. Yet such was the relief when we discovered how to keep harmful bacteria in check that for decades we threw antibiotics at them without restraint. Even now, doctors will admit to sometimes prescribing antibiotics just because a patient demands them (they are useless, for example, against viral infections). Now most of our weapons are blunt and we are running out of options.

You might imagine that, to keep up with this evolutionary arms race, pharmaceutical companies will have been churning out antibiotics at an increasingly frantic rate. The opposite is the case: over the past few decades they have all but given up looking for them. The number of new antibiotics approved by the US Food

and Drugs Administration has fallen steadily, from 16 in 1983-7 to five in 2003-7 and just two in 2008-12.

How come? Pharmaceutical companies will only put much effort into drug development only if they can make money: that’s a simple fact of business survival. A company isn’t going to make the huge investment of bringing a new antibiotic to market if doctors are just going to sit on it in order to delay resistance. As it is, some antibiotics don’t generate enough revenue to cover their research and development costs. It might be possible to boost the profit margins—for example, the US passed the Gain (Generating Antibiotic Incentives Now) Act in 2012 that introduces fast-track rules for getting new antibiotics improved and extends the period over which a company can enjoy exclusive marketing rights on them. But market mechanisms will always have their limits.

An alternative idea is to establish an international funding pot for drugs that can’t easily turn a profit. The non-profit organisation Incentives for Global Health wants to establish a “health impact fund” that rewards companies in proportion to the global effectiveness of such drugs. Prizes like Longitude 2014 can also help—last autumn the White House announced a similar \$20m prize for the development of a rapid test that can identify antibiotic-resistant infections.

Some researchers think the economic problems have been overplayed, however. Lewis says that the industry stopped working on antibiotics not because it couldn’t make them pay but because it failed with the science: it simply couldn’t come up with good drugs. It’s this inability to find good new candidate compounds, he says, that is the real bottleneck. How can we get through it?

Lewis and his collaborators have recently found one possible answer. They developed a plastic device they call an iChip, in which they could isolate individual soil bacteria in separate chambers simply by diluting soil fluid so that each drop contains only one cell on average. The iChip is then placed back in the soil, sealed with membranes that let nutrients in but don’t let cells out. Once each cell has grown into a substantial colony, each containing just a single species, they extract some cells and see if they will inhibit the growth of a pathogen like *Staphylococcus aureus*. This way, the Boston group identified an antibiotic produced by a newly identified species of soil bacteria. They call it teixobactin, and it will also attack tuberculosis bacteria. “There’s a good chance it will become a drug,” says Lewis. It will have to jump through many hoops first; but the bigger story is how it was found, for the iChip might open up a new world of candidate drug compounds.

It’s precisely because the soil and grime of the natural world is a soup of antimicrobial compounds that the bacteria they harbour tend to have a lot of resistance already. (In contrast, some pathogens that are mutant forms of our own gut bacteria, such as *E. coli*, have led more sheltered lives and are easier to hit.) This battery of resistance strategies is sometimes called the resistome, and it is poorly understood. If we knew more about it, such as the evasions that bugs develop and how they get transferred between species, we might find clues for how to overcome resistance or limit its spread.

Antibiotics typically come in families. If a chemical compound with a particular molecular structure does the job, the chances are that others with similar structures will be effective too—perhaps more so, or perhaps slipping under the radar of a resistance mechanism. For example, streptomycin, the first ►



antibiotic used against tuberculosis, belongs to a class of molecules called aminoglycosides, of which there are now many other antibacterial members. Streptomycin and its cousins work by disrupting a bacterium's ability to make proteins, by sticking to the protein-making machinery called the ribosome. That, then, is one potential target for antibiotics.

There has been a lot of talk in recent years about countering resistance by finding new targets: new weak spots to attack. But some experts are now sceptical about the value of that approach. "In my opinion way too much effort and money has been expended toward this goal with very, very little payback," says Harvard chemist Andrew Myers. Even if we find a new target after all that effort, bacteria might quickly develop resistance against it.

What we want are new chemical compounds to hit them in the old places. But how do you find them? The problem for all drug discovery is that the options are vast: the possible ways of combining atoms into molecules of even a very modest size are so numerous that we can never hope to explore more than a tiny fraction of this "chemical space." Many antibiotics have been found by using chemistry to make small modifications to natural molecules that have antibacterial properties: a strategy called semisynthesis, since the product is part "natural" and part "synthetic."

But that limits you to a tiny corner of chemical space. If you can find a way to make a natural antibiotic from scratch—by "total synthesis" from simple starting compounds—you can try out more modifications, and more significant ones at that. Total synthesis is the epitome of the organic chemist's art, but for many natural products it is very challenging, particularly if you want a synthetic route that makes enough of the stuff to be useful.

The potential gains are clear, though. There have been about a

half-dozen antibiotics of the family called tetracyclines approved for use in the past 60 years, and all were made by semisynthesis. But when in 2007 Myers' lab found a way to make tetracyclines by total synthesis, the number of candidates ballooned. The pharmaceutical company Tetrphase was formed in 2006 to exploit that success, and "made over 3,000 new drug candidates in short order," says Myers. Tetrphase now has a tetracycline-related compound in the last phase of clinical trials; according to Myers, "it is a serious broad-spectrum antibiotic that hits the bugs we are most concerned about."

As we come to understand more about the molecular-scale mechanisms of bacterial resistance, as computer methods get better at predicting how molecules interact, and as we become more skilled at making natural antibiotics from scratch, the search for new ones will become less scatter-shot and more rational. We might be able to design antibiotics rather than hoping to stumble across them.

But that needs a concerted effort on many fronts. Myers agrees with Lewis that the pharmaceutical industry's investment in antibiotic research and development has been woeful. There are signs that this might be changing—for example, in December the chemicals giant Merck bought Cubist, a pharmaceutical company working solely on antibiotics for resistant bacteria, and there is speculation that another major company, Roche, might acquire Tetrphase. Let's hope they're getting serious. Without better ways to fund and stimulate the basic research needed to discover and develop new candidate antibiotics, Myers says, "the consequences for society could be dire."

As a researcher in this area, of course he would say that. But I'm afraid he's right. ■



CULTURAL TOURS, PRIVATE VIEWS AND STUDY DAYS

Our visits are led by experts whose passion and authority on their subjects are equal to their sense of hospitality, attention to detail and above all, their sense of fun.

SELECTED TOURS 2015

IMPERIAL SPLENDOUR:
THE MOSAICS
OF RAVENNA

15 - 18 OCTOBER 2015
WITH CHARLES FREEMAN

TRUFFLE TIME:
THE ART &
GASTRONOMY
OF PIEDMONT

26 OCTOBER - 1 NOVEMBER 2015
WITH TOM DUNCAN

PATRICIANS & PATRONAGE:
FLORENCE &
THE EARLY MEDICI

29 OCTOBER - 2 NOVEMBER 2015
WITH PAULA NUTTALL

CARAVAGGIO & BERNINI:
THE GLORIES OF
BAROQUE ROME

5 - 9 NOVEMBER 2015
WITH TOM DUNCAN

ANTIQUITY EXPLORED:
THE GOLDEN AGE
OF ANCIENT ROME

12 - 16 NOVEMBER 2015
WITH CHRISTOPHER SMITH

To request a
brochure please
call 01869 811167,
email or visit
our website



The Pantheon Dome, Rome

CONTACT US

+44 (0) 1869 811167 | info@ciceroni.co.uk | www.ciceroni.co.uk



Copyright of Prospect is the property of Prospect Publishing and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.